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(54) Title: GASTRO RETENTIVE DELIVERY SYSTEM

(57) Abstract: The present invention is directed to pharmaceutical composition for the manufacture of a gastro retentive drug delivery system comprising a pharmaceutical formulation and an application condition of the same.

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GASTRO RETENTIVE DELIVERY SYSTEM

FIELD OF THE INVENTION

The present invention is directed to pharmaceutical compositions for the manufacture of a gastro retentive drug delivery system comprising a pharmaceutical formulation and a defined application condition of the same.

BACKGROUND OF THE INVENTION

For more than 20 years, development of gastric retained dosage forms was attempted resulting in only a limited number of promising technologies and products on the market.

Gastric retention of more than 6 hours still poses a considerable challenge to the pharmaceutical art.

Subject of the present invention is the development of a gastro retentive drug delivery system providing an extended residence time of the dosage form in the stomach of preferably more than 4 hours. Such a system is useful to improve the bioavailability and the duration of action of drugs.

DESCRIPTION OF THE INVENTION

The invention relates to a gastro retentive drug delivery system enabling a pharmaceutical formulation having an extended residence time in the stomach. Typically, the gastric emptying time is in fasted state in the range from 0-2 hours and in the fed state from 4-6 hours. Purpose of the present invention is to describe a drug delivery system for to provide a pharmaceutical formulation to stay in the stomach for at least 4, preferably 6 hours.

Surprisingly it was found that the sustained release formulations of the present invention show stomach residence times of more than 4 hours if taken in fed state. According to the present invention such a combination of a pharmaceutical formulation and a defined application scheme provides a new drug delivery platform technology with an interesting gastro retentive profile for many drugs.

The pharmaceutical formulation which is part of gastro retentive drug delivery system according to the invention has a defined minimum size and combines retarding, swelling and mucoadhesive properties. According to the invention the formulation comprises either one polymer having all three effects or two polymers, one providing the mucoadhesive property, the other one providing a retarding and swelling effect. Preferably the gastro retentive drug delivery system of the present invention comprises a gastro retentive tablet formulation of a defined minimum size, wherein the matrix comprises at least two water swelling polymers and wherein at least one of the at least two polymers is an anionic polymer.

The size of tablet refers to a tablet prior to application by the patient, if not otherwise stated.

The size of the tablet shall be defined according to the 3 dimensions in space, namely its length, its width and its height. It will be acknowledged that the skilled person in the art will not have difficulties in establishing the length, the width and the height. In case of unusual forms of the tablet, the body of such tablet shall be idealized to the closest mathematical body in order to define length, width and height. Examples for such idealized mathematical bodies are: cube, cuboid, tetrahedron, hexahedron, octahedron, dodecahedron, icosahedron, prism, ball, ellipsoid, paraboloid, cone, ring, sphere and the like. These idealized mathematical bodies also may be in a compressed shape.

Typically, the length of a body is the distance between the two subtending points at which the main axis of said body subtends the corresponding subtending surfaces areas of the body. The main axis usually is the medial axis of a shape, an axis around which a geometric rotation body rotates, a symmetrical axis or an optical axis. For the skilled person in the art it will be an easy to define a main axis of a tablet.

The width of the tablet shall be the longest distance between the two subtending points at which an axis of the body, which is perpendicular to the main axis, subtends the corresponding subtending surfaces areas of the body. The width of the body is equal or smaller than the length and equal or longer than the height.

Finally, the height or thickness is defined as the distance between the two subtending points at which an axis of the body, which is perpendicular to the main axis and perpendicular to the axis that defines the width, subtends the corresponding subtending surfaces areas of the body. The height of the body is equal or smaller than the width.

In less symmetrical bodies, the axis by which the width is defined and the axis by which the height is defined and the axis by which the length is defined need not touch each other, but may be displaced. The same applies for each pair of two axes.

The axes that define the length, the width and the height typically are perpendicular to each other.

In a cube or in a ball, the axes that define length, the width and the height are equally long, perpendicular to each other and meet in one point.

In cuboid, the three axes are not all equally long, but again perpendicular to each other and meet in one point.

According to the invention the tablet is characterised in that the length and the width have independent from each other a minimum length which corresponds to at least 7/12, more preferably at least 8/12, more preferably at least 9/12, more preferably at least 10/12, more preferably at least 11/12, more preferably at least 12/12, more preferably at least 13/12, more preferably at least 14/12, more preferably at least 15/12, more preferably at least 16/12, more preferably at least 17/12, more preferably at least 18/12, more preferably at least 19/12, more preferably at least 20/12 of the patient's pyloric diameter.

The human pyloric diameter in average is 12 mm +/- 7 mm. All relations of the length or the width to human pyloric diameter shall refer to the average amount of 12 mm in order to calculate absolute amounts of the length and the width.

The tablet for a human patient of normal adult size is characterised in that its length and its width have independent from each other a minimum length of at least 6 mm, preferably at least 7 mm, preferably at least 8 mm, preferably at least 9 mm, preferably at least

preferably 10 mm, preferably at least 11 mm, preferably at least 12 mm, preferably at least 13 mm, preferably at least 14 mm, preferably at least 15 mm, preferably at least 16 mm, preferably at least 17 mm, preferably at least 18 mm, preferably at least 19 mm, preferably at least 20 mm.

Values are preferred in that the length is longer than the width. The length preferably is at is at least 9 mm, more preferably at least 11 mm. The width is at least 6 mm, preferably at least 7 mm long.

In these embodiments, neither the length nor the width have a maximally preferred length of more than 50 mm, preferably not more 40 mm, preferably not more than 25 mm, preferably not more than 20 mm.

For human children, with smaller pyloric diameter, the length and width of such tablet are correspondingly smaller.

In case the tablet according to the invention is used for an animal the size may differ from that of a human patient according to the ratio of length/width to the animal's pyloric diameter. In case of an animal as patient, the animal preferably is selected from the group of horses, cows, pigs, dogs, cats, rabbits, bunnies, chicken, more preferably it is selected from the group of horses and cows.

In a preferred embodiment of the invention the tablet for a human patient is a round shaped tablet, i.e. a compressed ball having a diameter of at least 9, more preferably at least 11 mm.

In another preferred embodiment, the tablet is an oval shaped tablet having a length of at least 15 mm and a width of at least 7 mm.

Preferred minimum values width x length, both in mm, are:
(7x12); (7x13); (7x14); (7x15); (7x16); (7x17); (7x18); (7x19); (7x20);
(8x12); (8x13); (8x14); (8x15); (8x16); (8x17); (8x18); (8x19); (8x20);
(9x12); (9x13); (9x14); (9x15); (9x16); (9x17); (9x18); (9x19); (9x20);

(10x12); (10x13); (10x14); (10x15); (10x16); (10x17); (10x18); (10x19); (10x20); (11x12); (11x13); (11x14); (11x15); (11x16); (11x17); (11x18); (11x19); (11x20); (12x12); (12x13); (12x14); (12x15); (12x16); (12x17); (12x18); (12x19); (12x20); (13x13); (14x14); (15x15); (16x16); (17x17); (18x18); (19x19); (12x20).

Each pair of which independently is preferred.

The height preferably is at least 1 mm, 2 mm, 3, mm, 4, mm, 5, mm, 6 mm, 7, mm, 8, mm, 9 mm, 10 mm.

To provide a mucoadhesive effect, the invention makes use of "retarding polymers with mucoadhesive properties", preferably anionic polymers. Without limitation, such polymers may be selected from the group of carboxyalkylcelluloses such as carmellose sodium or carmellose calcium, chondroitin sulfate, acrylic acid polymerisate, pectin, alginates, carrageenans, chitin derivates such as chitosan, preferably acrylic acid polymerisate or chitosan. Among the preferred anionic polymer is an optionally crosslinked acrylic acid polymer. As acrylic acid polymerisate one may use one of the carbomer or carbopol® series, having high molecular weights. Particularly preferred are for example carbomer 941 (carbopol® 71 G, carbopol® 971) and carbomer 934 (carbopol® 974). The content of the optionally crosslinked acrylic acid polymer in the matrix is from about 0.1 wt.-% to about 40 wt.-% and preferably from about 0.1 wt.-% to about 20 wt.-%.
The absolute amount of the retarding polymer preferably is between 0.5 and 600 mg, more preferably 0.5 to 400 mg, more preferably 0.5 to 200 mg or 0.5 to 100 mg. Even more preferred values are between 2 mg and 150 mg, more preferred between 2 mg and 100 mg, more preferably between 2 mg and 50 mg, more preferably between 2 mg and 25 mg.

In one embodiment the amount is between 2 mg to 600 mg, in another embodiment between 3,9 mg and 400 mg, in another embodiment between 4 and 340 mg, in another embodiment between 4 mg and 340 and still in another embodiment between 5 mg and 300 mg.

To provide a retarding or an increased retarding effect, the formulation according to the invention may comprise a "swelling retarding polymer", a water swelling substantially

neutral polymer. Without limitation, such swelling retarding polymers may be selected from the group of alkylcelluloses, such as, methylcellulose; hydroxyalkylcelluloses, for example, hydroxymethylcellulose (HPMC), hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose; hydroxyalkyl alkylcelluloses, such as, hydroxyethyl methylcellulose and hydroxypropyl methylcellulose; other natural, semi-synthetic, or synthetic di-, oligo- and polysaccharides such as galactomannans, tragacanth, agar, guar gum, and polyfructans; ammonio methacrylate copolymers; polyvinylalcohol; polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate; combinations of polyvinylalcohol and polyvinylpyrrolidone; polyalkylene oxides such as polyethylene oxide and polypropylene oxide; copolymers of ethylene oxide and propylene oxide; preferably polyethylene oxide and cellulose ether derivatives such as hydroxypropyl methylcellulose and hydroxypropylcellulose, most preferred hydroxypropyl methylcellulose.

Such neutral polymer swells upon contact with aqueous fluid following administration, resulting in a viscous, drug release regulating gellayer. The viscosity of the polymer preferably ranges from 50 to 100,000 mPa.s (apparent viscosity of a 2% aqueous solution at 20°C.).

Preferably, the amount of water swelling polymer in the present formulation ranges from about 10 to about 80% by weight.
The absolute amount of the swelling polymer preferably is between 10 and 1200 mg, preferably between 20 mg and 800 mg, more preferably between 40 mg and 700 mg, more preferably between 50 mg and 400 mg.

In one embodiment the amount is between 20 mg to 1200 mg, in another embodiment between 39 mg and 800 mg, in another embodiment between 40 and 680 mg, in another embodiment between 50 mg and 600 mg.

Preferably, the amount of the swelling polymer is adjusted in that at least the length of the tablet grows in the fed stomach to at least 11/12, more preferably at least 12/12, more preferably at least 13/12, more preferably at least 14/12, more preferably at least 15/12, of the pyloric diameter of the patient, which in average for a human being is at least 12 mm.

Preferably the tablet reaches the aforementioned length within less than 3 hours, preferably within less than 2 hours, more preferably within less than 90 minutes and more preferably within less than 60 minutes.

More preferably, the amount of the swelling polymer is adjusted in that in addition to the growing of the length, the width of the tablet grows in the fed stomach to at least 8/12, more preferably at least 9/12, more preferably at least 10/12, more preferably at least 11/12, more preferably at least 12/12, of the diameter of pyloric diameter of the patient, which in average for a human being is at least 12 mm.

Among the substantially neutral polymers hydroxypropylcellulose and hydroxypropyl methylcellulose are preferred.

Different viscosity grades of hydroxypropylcellulose and hydroxypropyl methylcellulose are commercially available. Hydroxypropyl methylcellulose (HPMC) preferably used in the present invention has a viscosity grade ranging from about 50 mPa.s to about 100,000 mPa.s, in particular ranging from about 75 mPa.s to about 20,000 mPa.s and most in particular a viscosity grade of about 100 mPa.s to about 15,000 mPa.s (apparent viscosity of a 2% aqueous solution at 20°C.), e.g. hypromellose 2910, 2208 or 2206 (DOW, Antwerp, Belgium). HPMC type 2208 contains 19-24% by weight methoxy and 4-12% by weight hydroxypropoxy substituents.

Hydroxypropylcellulose having a viscosity higher than 300 mPa.s (apparent viscosity of a 10% aqueous solution at 20°C) is preferred, in particular hydroxypropylcellulose having a viscosity in the range from about 300 to about 30000 mPa.s, preferably from 4000 to 6500 mPa.s (2% aqueous solutions), e.g. the Klucel series such as Klucel M (Hercules, Wilmington, USA).

According to a preferred embodiment of the present invention the matrix of a gastro retentive tablet formulation comprises or essentially consists of hydroxypropyl methylcellulose, such as hypromellose, and further excipients. The amount of hydroxypropyl methylcellulose is preferably in the range from 10 to 80%, particularly preferred from 15 to 65% most preferred from 20 to 50% by weight. The amount of further

excipients is preferably in the range from 80 to 25%, particularly preferred from 75 to 35%, most preferred from 65 to 45% by weight.

Such systems with mucoadhesive, retarding and swelling properties are useful to extend the gastric residence time by adhering them to the gastric mucous membrane. Even though some of the mucoadhesive polymers are effective at producing bioadhesion, it is very difficult to maintain a residence time over several hours with this effect alone because of the rapid turnover of mucus in the gastrointestinal tract.

When using a combination of a neutral and anionic polymer, the ratio of said polymers also may influence the gastro retentive profile of the preparation. Accordingly, such combination facilitates control of the gastro retentive profile of the preparation at will and it will be perspicuous for the skilled person in the art, that the gastro retentive profile may be adjusted via the ratio of said polymers, which is another benefit of the present invention.

According to a preferred embodiment of the present invention a tablet formulation is provided having a matrix that comprises or essentially consists of hydroxypropyl methylcellulose, acrylic acid polymerisate and further excipients. The amount of hydroxypropyl methylcellulose is preferably in the range from 10 to 80%, particularly preferred from 15 to 65%, most preferred from 20 to 50% by weight. The amount of acrylic acid polymerisate is preferably as above-mentioned. The amount of additional excipients is preferably in the range from 80 to 25% particularly preferred from 75 to 35%, most preferred from 65 to 45% by weight.

The tablet formulation of the present invention optionally comprises an active ingredient. Such active ingredient may

- show pH-dependent solubility and/or
- show a limited absorption window in the gastrointestinal tract and/or
- be intended for local treatment in the stomach or the small intestine and/or
- show low stability in intestinal fluids and/or
- degrades by enzymes/bacteria present in the intestine.

However, the tablet formulation also may be a placebo, meaning that the formulation does not comprise an active ingredient. In one embodiment the tablet excludes pramipexole as active ingredient. In another embodiment the gastro retentive delivery system according to the invention comprises pramipexole.

The formulation according to the invention optionally comprise further excipients, i.e. pharmaceutically acceptable formulating agents, in order to promote the manufacture, compressibility, appearance and taste of the preparation. These formulating agents comprise, for example, diluents or fillers, glidants, binding agents, granulating agents, anti-caking agents, lubricants, flavors, dyes and preservatives. Other conventional excipients known in the art can also be included.

The filler may be selected from soluble fillers, for example, sucrose, lactose, in particular lactose monohydrate, trehalose, maltose, mannitol and sorbitol. Different grades of lactose can be used.

In case of a water soluble active ingredient, more preferably water insoluble fillers, such as starch and starch derivates preferably other than pregelatinized starch, e.g. corn starch, potato starch, rice starch or wheat starch, microcrystalline cellulose, dibasic calcium phosphate dihydrate and anhydrous dibasic calcium phosphate, preferably corn starch, can be used in addition or instead of the water soluble fillers. The total weight percentage of filler ranges between about 5% and about 75% by weight.

A glidant can be used to improve powder flow properties prior to and during tableting and to reduce caking. Suitable glidants include colloidal silicon dioxide, talc, magnesium trisilicate, powdered cellulose, talc, tribasic calcium phosphate and the like. Colloidal silicon dioxide is preferably included as a glidant in an amount up to about 2%, preferably about 0.2% to about 0.8%, by weight of the tablet.

A lubricant can be used to enhance release of a tablet from apparatus on which it is formed, for example by preventing adherence to the face of an upper punch ("picking") or lower punch ("sticking"). Suitable lubricants include magnesium stearate, calcium stearate, canola oil, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, mineral oil, poloxamer, polyethylene glycol, polyvinyl alcohol, sodium benzoate, sodium lauryl

sulfate, sodium stearyl fumarate, stearic acid, zinc stearate and the like. In one embodiment, magnesium stearate is included as a lubricant in an amount of about 0.1% to about 5%, preferably about 0.5% to about 2%, by weight of the tablet.

Among the optional formulating agents that further may be comprised in the matrix formulation there may be mentioned agents such as polyvidone; copovidone; starch; acacia; gelatin; seaweed derivatives, e.g. alginic acid, sodium and calcium alginate; cellulose, preferably microcrystalline cellulose, cellulose derivatives, e.g. ethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, having useful dry or wet binding and granulating properties; and antiadherents such as talc and magnesium stearate.

The expression "consisting essentially" is understood in the sense that it does not in principle exclude the presence, in addition to the mandatory components mentioned, of other components, the presence of which does not affect the essential nature of the formulation.

In a preferred embodiment of the present invention the tablet formulation with gastro retentive properties is provided preferably having the following composition:

active ingredient	0.01 – 50 % by weight
swelling retarding polymer	10 to 80 % by weight, preferably 20 - 50 % by weight
retarding polymers with mucoadhesive properties	0.1 – 40 % by weight, preferably 0.1 - 20 % by weight

In another preferred embodiment of the present invention the formulation tablet with gastro retentive properties is provided preferably having the following composition:

active ingredient	0.05 to 5% by weight
water swelling polymer(s)	10 to 75% by weight
acrylic acid polymerisate	0 to 25% by weight
optional further excipient(s)	ad 100% by weight.

Therefore, a particularly preferred tablet formulation according to the invention consists of 0.1 to 35% by weight of active ingredient thereof;

25 to 65% by weight of hydroxypropyl methylcellulose;
0 to 40% by weight of carboxymethylcellulose sodium;
0 to 75% by weight of corn starch other than pregelatinized starch;
0.1 to 15% by weight of acrylic polymerisate, preferably carbomer 941;
0.5 to 50% by weight of excipients, preferably selected from the group consisting of colloidal silicon dioxide, magnesium stearate, lactose monohydrate, mannitol, microcrystalline cellulose, dibasic anhydrous calcium phosphate, hydroxyproylcellulose, povidone, copovidone, talc, macrogols, sodium dodecylsulfate, iron oxides and titanium dioxide.

According to the present invention starch, preferably other than pregelatinized starch, preferably corn starch if present, may impart several functions at the same time such as filler, glidant, and the like. However, it may be preferred to exclude starch completely from the tablet formulation according to the present invention, which may be replaced by one or more of the above-mentioned other excipient(s).

It is preferred that no coating is present on the tablet formulation according to the present invention. However, the tablet of the invention may comprise a nonfunctional coating. A nonfunctional coating can comprise a polymer component, for example HPMC, optionally with other ingredients, for example one or more plasticizers, colorants, etc. The term "nonfunctional" in the present context means having no substantial effect on release properties of the tablet, and the coating serves another useful purpose. For example, such a coating can impart a distinctive appearance to the tablet, provide protection against attrition during packaging and transportation, improve ease of swallowing, and/or have other benefits. A nonfunctional coating should be applied in an amount sufficient to provide complete coverage of the tablet. Typically an amount of about 1% to about 10%, more typically an amount of about 2% to about 5%, by weight of the tablet as a whole, is suitable.

The tablets of the present invention can be of any suitable size and shape, for example round, oval, polygonal or pillow-shaped, and optionally bear nonfunctional surface markings. According to the present invention it is preferred that the extended release tablets are white to off-white and of oval or round, biconvex, shape.

In another preferred embodiment of the invention a tablet is provided having weight in the range of 200 mg to 1500 mg, preferably 390 mg to 1000 mg, more preferably 400 mg to 850 mg and even more preferably of 500 mg to 750 mg.

The gastro retentive delivery system according to the invention comprises the tablets as hereinbefore described together with an information of how to apply the same for to provide the gastro retentive effect.

Accordingly, tablets of the invention can be packaged in a container, accompanied by package insert providing pertinent information such as, for example, dosage and administration information, contraindications, precautions, drug interactions and adverse reactions.

However, the aforementioned approach directed to the composition of the pharmaceutical formulation according to the invention alone may not provide the herein disclosed effect.

It is recommended to apply the tablets of the drug delivery system of the present invention in fed state, meaning after meal. This is as it has been observed that food, particularly fatty acids, prevents emptying of the stomach.

In the context of the present invention the term "fed state" means that patients take the drug at maximum 4 hours, preferably at maximum 3 hours, more preferably at maximum 2 hours, even more preferably at maximum 1 hour, even more preferably at maximum 30 minutes and most preferably just after an ordinary meal (breakfast, lunch, dinner). In an alternative preferred embodiment the patients may take the tablet while eating. The opposite of fed state is an empty stomach, meaning that the last meal was taken at least 4 hours, more preferably at least 5 hours, more preferably at least 6 hours ago.

Within the context of the present invention "fed" or "fed state" preferably means that a tablet is taken during, just before or just after a meal, more preferably during or just after a meal.

Furthermore, the present invention is preferably directed to a method of manufacturing the extended release tablet formulations via a direct compression process comprising the steps of

(1) producing an active ingredient trituration by preblending it with a portion of water swelling polymer(s) and/or further excipient(s) in a mixer;

(2) premixing the active ingredient trituration of step (1), the main portion of the water swelling polymer(s) and/or excipients in a mixer to obtain a pre-mixture;

(3) optionally dry screening the pre-mixture through a screen in order to segregate cohesive particles and to improve content uniformity;

(4) mixing the pre-mixture of step (2) or (3) in a mixer, optionally by adding remaining excipients to the mixture and continuing mixing; and

(5) tableting the final mixture by compressing it on a suitable tablet press to produce matrix tablets.

Also other processes can be applied to the manufacturing of tablets according to the invention, like conventional wet granulation and roller compaction. In case of wet granulation the active ingredient may be granulated with suitable fillers, like e.g. starches other than pregelatinized starch, microcrystalline cellulose, lactose monohydrate or anhydrous dibasic calcium phosphate, and wet binding agents, like e.g. hydroxypropyl methylcellulose, hydroxypropylcellulose, povidone, copovidone, and starch paste, leading to a active ingredient concentrate, which after drying and dry screening is mixed with the main fraction of gel forming excipients, like all the above described retarding principles.

In case of roller compaction, or in other words dry granulation, either a premix of active ingredient with part of the excipients used in the direct compression process, or the complete mixture containing all excipients, is processed through a conventional roller compactor to form ribbons, which are thereafter screened down to granules which are finally mixed with other excipients, like glidants, lubricants and antiadherents.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates a preferred embodiment of the manufacturing process with reference to a flow diagram wherein the manufacture of the extended release tablets of Examples 4 and 5 are exemplarily shown. Figure 1 shows the detailed process steps and the in process controls performed.

Process step (1) is directed to the active ingredient trituration, where the active ingredient is preblended with a portion of the polymer, in this case hydroxypropyl methylcellulose, in a commonly known mixer. In the flow chart a Turbula free-fall mixer or blender is used. The mixing time is several minutes, in the present case preferably 10 min.

In process step (2) according to the flow chart a premixing is performed, wherein the active ingredient trituration and the main portion of the water swelling polymer(s) and excipients are premixed for several minutes to obtain a pre-mix. In the present case the main portion of hydroxypropyl methylcellulose (hypromellose), corn starch, carbomer 941 and colloidal silicon dioxide are premixed for 5 min. in the above-mentioned Turbula mixer or blender.

According to the following process step (3) a dry screening may optionally take place. The pre-mixture may be manually screened through a screen, for example a 0.8 mm mesh size screen, in order to segregate cohesive particles and to improve content uniformity.

In the subsequent process step (4) the main mixing step is performed according to which the components are mixed for several minutes, preferably 5 min. in the Turbula mixer after screening. Optionally further excipients may be added at this time, in the flow chart the component magnesium stearate is added to the main mixture, and further mixing for several minutes, e.g. 3 min., in the Turbula mixer is performed (final mixing) to obtain the final mixture.

Process step (5) of the process according to the present invention is the tableting. The final mixture is compressed on a suitable tablet press to produce, for example, oval shaped matrix tablets (ER tablets = extended release tablets). In order to control and maintain the

required quality the obtained matrix tablets are subjected to the following in-process controls: tablet mass, hardness, tablet height and friability.

The obtained tablets of the present invention may then be filled, for example, into High Density Polyethylene (HDPE) bottles. The bottles are closed tightly with screw caps and appropriately labelled, whereby all packaging and labelling activities are performed according to cGMP regulations. Alternatively, a blister type packaging can be used, e.g. using aluminium/aluminium foil blisters.

Furthermore, the tablets of the present invention may be manufactured via a direct compression, wet or dry granulation process.

FORMULATION EXAMPLES

Placebo tablets were prepared with the following composition

Hypromellose 2208	112.50 mg
Maize starch	114.75 mg
Carbomer 941	15.00 mg
Iron oxide black	5.00 mg
Colloidal anhydrous silica	1.50 mg
Magnesium stearate	1.25 mg
Total weight placebo tablet	250.00 mg

Hypromellose 2208	225.0 mg
Maize starch	249.5 mg
Carbomer 941	15.0 mg
Iron oxide black	5.0 mg
Colloidal anhydrous silica	3.0 mg
Magnesium stearate	2.5 mg
Total weight placebo tablet	500.0 mg

Hypromellose 2208	315.0 mg
Maize starch	321.3 mg
Carbomer 941	42.0 mg

Iron oxide black	14.0 mg
Colloidal anhydrous silica	4.2 mg
Magnesium stearate	3.5 mg
Total weight placebo tablet	700.0 mg

Further examples with active ingredients are

Active ingredient	0.750 mg
Hypromellose 2208 (Methocel K 15 M)	157.500 mg
Corn starch	183.700 mg
Carbomer 941 (Carbopol® 71 G)	3.500 mg
Colloidal Silicon dioxide	2.800 mg
Magnesium stearate	1.750 mg
Total weight matrix tablet	350.000 mg

Active ingredient	4.500 mg
Hypromellose 2208 (Methocel K 15 M)	225.000 mg
Corn starch	250.000 mg
Carbomer 941 (Carbopol® 71 G)	15.000 mg
Colloidal Silicon dioxide	3.000 mg
Magnesium stearate	2.500 mg
Total weight matrix tablet	500.000 mg

Active ingredient	0.750 mg
Hypromellose 2208 (Methocel K 15 M)	157.500 mg
Corn starch	174.600 mg
Carbomer 941 (Carbopol® 71 G)	14.000 mg
Colloidal Silicon dioxide	1.400 mg
Magnesium stearate	1.750 mg
Total weight matrix tablet	350.000 mg

Active ingredient	1.500 mg

Hypromellose 2208	315.000 mg
Corn starch	349.200 mg
Carbomer 941	28.000 mg
Colloidal Silicon dioxide	2.800 mg
Magnesium stearate	3.500 mg
Total weight matrix tablet	700.000 mg

Active ingredient	0.750 mg
Hypromellose 2208 (Methocel K 15 M)	180.000 mg
Carboxymethylcellulose sodium	100.000 mg
Lactose monohydrate (200 mesh)	50.000 mg
Microcrystalline cellulose (grade PH 101)	65.750 mg
Colloidal silicon dioxide	1.500 mg
Magnesium stearate	2.000 mg
Total weight matrix tablet	400.000 mg

Active ingredient	100.000 mg
Hydroxypropylcellulose	270.000 mg
Carboxymethylcellulose sodium	60.000 mg
Lactose monohydrate (200 mesh)	50.000 mg
Microcrystalline cellulose (grade PH 101)	99.000 mg
Carbomer 941 (Carbopol® 71 G)	6.000 mg
Colloidal silicon dioxide	3.000 mg
Magnesium stearate	12.000 mg
Total weight matrix tablet	600.000 mg

Active ingredient	0.750 mg
Hypromellose 2208 (Methocel K 15 M)	175.000 mg
Carboxymethylcellulose sodium	87.500 mg

Lactose monohydrate (200 mesh)	45.500 mg
Microcrystalline cellulose (grade PH 101)	24.100 mg
Carbomer 941 (Carbopol® 71 G)	14.000 mg
Colloidal silicon dioxide	1.400 mg
Magnesium stearate	1.750 mg
Total weight matrix tablet	350.000 mg

Active ingredient	200.00 mg
Hypromellose 2208 (Methocel E50 LV)	300.00 mg
Lactose monohydrate	190.00 mg
Carbomer 941 (Carbopol® 71 G)	37.500 mg
Colloidal silicon dioxide	7.50 mg
Magnesium stearate	15.00 mg
Total weight matrix tablet	750.000 mg

Active ingredient	100.00 mg
Hypromellose 2910 (Methocel E50 LV)	100.00 mg
Microcrystalline cellulose	215.00 mg
Sodium alginate	25.00 mg
Organic acid	50.00 mg
Colloidal silicon dioxide	2.50 mg
Magnesium stearate	7.50 mg
Total weight matrix tablet	500.00 mg

Active ingredient	100.00 mg
Hypromellose 2208 (Methocel K 100 LV)	150.00 mg
Microcrystalline cellulose	235.00 mg

Carbomer 941 (Carbopol® 71 G)	5.00 mg
Colloidal silicon dioxide	2.50 mg
Magnesium stearate	7.50 mg
Total weight matrix tablet	500.000 mg

GASTRO RETENTIVE EFFECT

The gastro retentive effect was proven with magnetically marked tablets of the aforementioned type (Placebo tablet of 250 mg and 500 mg weight with incorporation of Fe_3O_4-Magnetit.)

The tablets were applied to patients and the GI-transit was monitored via the magnetic properties of the tablets. The decline of aligned magnetic moment was correlated with in vivo disintegration.

In a randomized, open, four-way changeover magnetic marker monitoring study the gastro-intestinal transit and in vivo disintegration process of two differently sized extended release matrix tablets containing Fe_3O_4 (E172) was evaluated at 8 healthy volunteers (4 males 4 females). The volunteers were given the magnetically marked tablets in fasted and fed state.

It was observed during routine in-vitro dissolution tests that the gastro retentive dosage form starts to swell after contact with fluids and that it starts to float on the top of the dissolution media. The swollen tablets have obviously a lower density than water.

The results showed that in particular tablets show a gastro retentive effect of more than 4 hours if taken in fed state. So it could be shown that the mean residence time in fed state was nine times longer than given without a meal.

Additionally it could be shown that while round tablets of 9 mm diameter (= length and width are each 9 mm) and 4.7 mm height with a weight of 250 mg (=small tablet) already had a residence time in the stomach of more than 5 hours if taken after meal, larger tablets of oval shape and 16.2 mm length, 7.9 mm width and 5.3 mm height, with a weight of 500 mg (=large tablet) even showed a residence time of more than 8 hours when taken under the same conditions.

The average results measured for 8 adult patients are outlined in the following table:

Tab. 1:Results for gastric residence time of the small tablet given with or without food:

	Mean residence time
Fasted state	37 minutes
Fed state	325 minutes

Tab. 2: Results for the gastric residence time of the small and large tablet given after a meal:

	Mean residence time
Small tablet	325 minutes
Large tablet	570 minutes

Accordingly, the results show that the large tablet stays significantly longer in the stomach.

CLAIMS

1. A tablet comprising at least one active ingredient, characterised in that at least the length of the tablet in the state prior to application is at least 7/12, more preferably at least 8/12, more preferably at least 9/12, more preferably at least 10/12, more preferably at least 11/12, more preferably at least 12/12, more preferably at least 13/12, more preferably at least 14/12, more preferably at least 15/12, more preferably at least 16/12, more preferably at least 17/12, more preferably at least 18/12, more preferably at least 19/12, more preferably at least 20/12 of the patient's pyloric diameter and after swallowing in fed state the length of the tablet grows in the stomach to at least 11/12, more preferably at least 12/12, more preferably at least 13/12, more preferably at least 14/12, more preferably at least 15/12, of the patient's pyloric diameter.

2. A tablet according to claim 1, characterised in that its width, which is not larger than the length, in the state prior to application is at least 7/12, more preferably at least 8/12, more preferably at least 9/12, more preferably at least 10/12, more preferably at least 11/12, more preferably at least 12/12, more preferably at least 13/12, more preferably at least 14/12, more preferably at least 15/12, more preferably at least 16/12, more preferably at least 17/12, more preferably at least 18/12, more preferably at least 19/12, more preferably at least 20/12 of the patient's pyloric diameter and after swallowing in fed state the width grows in the stomach to at least 8/12, more preferably at least 9/12, more preferably at least 10/12, more preferably at least 11/12, more preferably at least 12/12, of the patient's pyloric diameter.

3. A tablet according to any of claims 1 or 2, characterised in that it comprises 0.01 – 50 % by weight of active ingredient, 10 to 80 % by weight, preferably 20 - 50 % by weight of a swelling retarding polymer, 0.1 – 40 % by weight, preferably 0.1 - 20 % by weight of retarding polymers with mucoadhesive properties.

4. A tablet comprising at least one active ingredient, characterised in that at least the length of the tablet in the state prior to application is at least 7 mm, preferably at least 8 mm, preferably at least 9 mm, preferably at least preferably 10 mm, preferably at least 11 mm,

preferably at least 12 mm, preferably at least 13 mm, preferably at least 14 mm, preferably at least 15 mm, preferably at least 16 mm, preferably at least 17 mm, preferably at least 18 mm, preferably at least 19 mm, preferably at least 20 mm and it comprises 0.01 – 50 % by weight of active ingredient, 10 to 80 % by weight, preferably 20 - 50 % by weight of a swelling retarding polymer, 0.1 – 40 % by weight, preferably 0.1 - 20 % by weight of retarding polymers with mucoadhesive properties.

5. A tablet according to claim 4, characterised in that its width, which is not larger than the length, in the state prior to application is at least 7 mm, preferably at least 8 mm, preferably at least 9 mm, preferably at least preferably 10 mm, preferably at least 11 mm, preferably at least 12 mm, preferably at least 13 mm, preferably at least 14 mm, preferably at least 15 mm, preferably at least 16 mm, preferably at least 17 mm, preferably at least 18 mm, preferably at least 19 mm, preferably at least 20 mm.

6. A tablet according to any of claims 1 to 5, characterised in that the retarding polymer is an anionic polymer.

7. A tablet according to claim 6, characterised in that the retarding polymer, preferably is selected from the group of carboxyalkylcelluloses, chondroitin sulfate, acrylic acid polymerisate, pectin, alginates, carrageenans, chitin derivates.

8. A tablet according to any of claims 1 to 7, characterised in that the swelling retarding polymer is a water swelling substantially neutral polymer.

9. A tablet according to claim 8, characterised in that the swelling retarding polymer, preferably is selected from the group of alkylcelluloses, hydroxyalkylcelluloses; hydroxyalkyl alkylcelluloses, natural, semi-synthetic, or synthetic di-, oligo- and polysaccharides; ammonio methacrylate copolymers; polyvinylalcohol; polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate; combinations of polyvinylalcohol and polyvinylpyrrolidone; polyalkylene oxides; copolymers of ethylene oxide and propylene oxide; and cellulose ether derivatives.

10. A tablet according to any of claims 1 to 9, characterised in that it further comprises excipients, preferably selected from the group of diluents, fillers, glidants, binding agents, granulating agents, anti-caking agents, lubricants, flavors and dyes.

11. Gastro retentive delivery system providing an extended residence time of a tablet in the stomach of preferably more than 4 hours, characterised in that it comprises at least one tablet according to any of claims 1 to 10 and an information according to which the tablet is to be applied in fed state.

12. Gastro retentive delivery system according to claim 11, characterised in that the information is a booklet which physically directly or indirectly is linked with the at least one tablet.

13. Gastro retentive delivery system according to claim 11, characterised in that the information is a booklet which together with one or more tablets or a package of tablets is part of a box, preferably a folded box.

14. Use of a tablet according to any of claims 1 to 10 for the allocation of a gastro retentive delivery system according to any of claims 11 to 13 to a patient.

15. Use of a tablet according to any of claims 1 to 10 for the manufacture of a gastro retentive delivery system for a patient providing an extended residence time of the tablet in the stomach of preferably more than 4 hours, characterised in that the tablet is to be taken in fed state.

16. Use according to any of claims 14 and 15, characterised in that the patient is a human being.

17. Use according to any of claims 14 and 15, characterised in that the patient is a human adult.

18. Use according to any of claims 14 and 15, characterised in that the patient is a human child.

19. Use according to any of claims 14 and 15, characterised in that the patient is an animal, preferably selected from the group of horses, cows, pigs, dogs, cats, rabbits, bunnies, chicken.

20. Method of providing a residence time of a tablet in a patient's fed stomach of preferably more than 4 hours, characterised in that a patient is given a tablet according to any of claims 1 to 10.

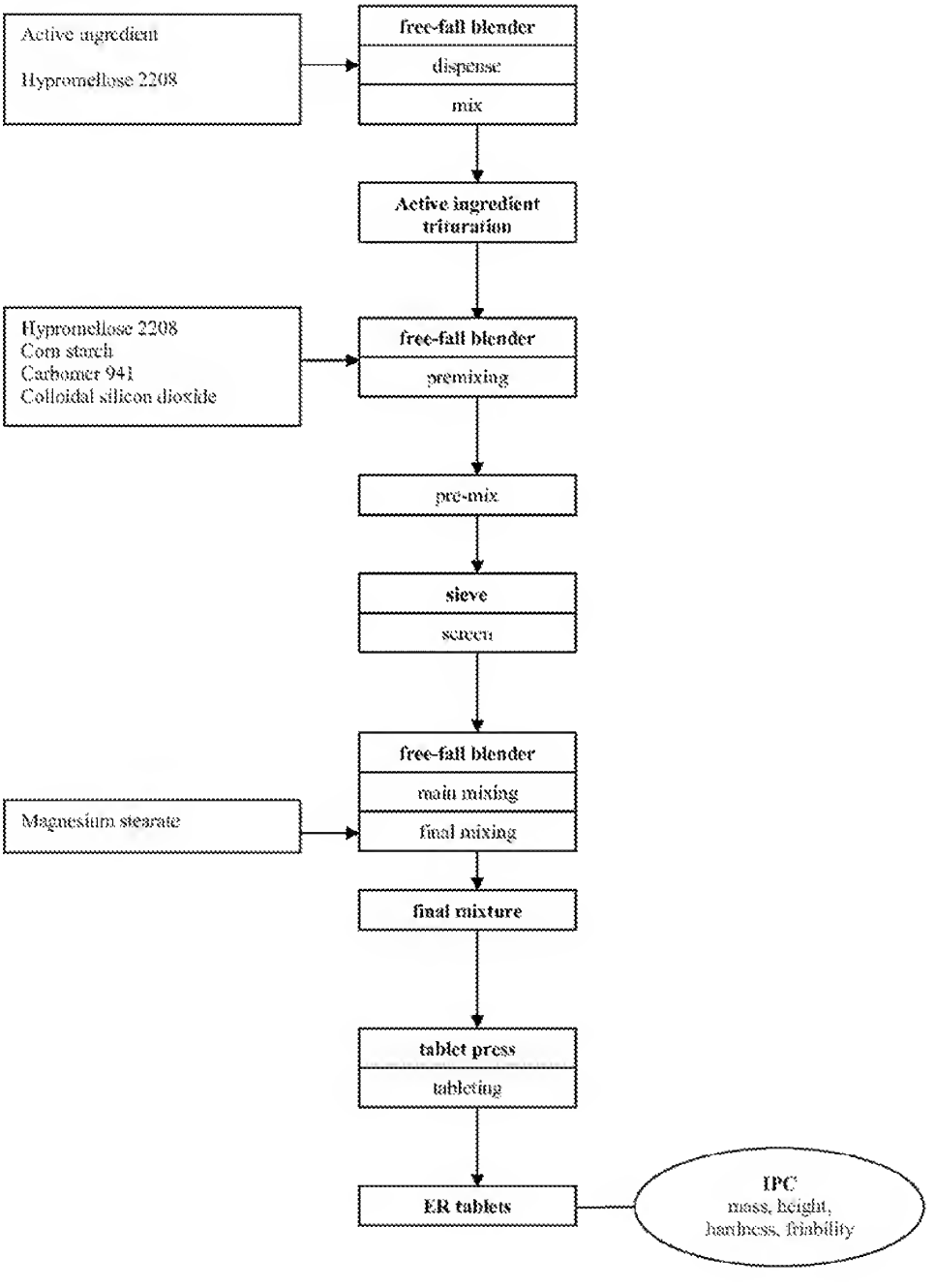
21. Method according to claim 20, characterised in that the patient is a human being.

22. Method according to claim 20, characterised in that the patient is a human adult.

23. Method according to claim 20, characterised in that the patient is a human child.

24. Method according to claim 20, characterised in that the patient is an animal, preferably selected from the group of horses, cows, pigs, dogs, cats, rabbits, bunnies, chicken.

Fig. 1


Active ingredient
Hypromellose 2208
free-fall blender
dispense
mix
Active ingredient trituration
Hypromellose 2208
Corn starch
Carbomer 941
Colloidal silicon dioxide
free-fall blender
premixing
pre-mix
sieve
screen
free-fall blender
main mixing
final mixing
Magnesium stearate
final mixture
tablet press
tableting
ER tablets
IPC
mass, height, hardness, friability

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/057738

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, FSTA, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	NUR A O ET AL: "CAPTOPRIL FLOATING AND/OR BIOADHESIVE TABLETS: DESIGN AND RELEASE KINETICS" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 9, no. 26, 2000, pages 965-969, XP008002146 ISSN: 0363-9045 page 965 page 966, paragraph 3 figure 1 table 1	1-24
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2007	29/10/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schüle, Stefanie

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	ELKHESHEN ET AL.: "In vitro and in vivo Evaluation of Floating Controlled Release Dosage Forms of Verapamil Hydrochloride" PHARM. IND., vol. 66, no. 11, 2004, pages 1364-1372, XP008076033 page 1366 page 1367, paragraph 3.1.1	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/057738

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14 and 20-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/057738

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